Validation of Surrogate Endpoints from Multiple Trials

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DATA

4 randomized multicenter trials in advanced ovarian cancer

Ovarian Cancer Meta-Analysis Project (1991)

Z: ***Two treatment modalities***

- 0: cyclophosphamide plus cisplatin (CP)
- 1: cyclophosphamide plus adriamycin plus cisplatin (CAP)

T: ***(Log of) Survival time***

- continuous
- Time in weeks from randomization to death from any cause

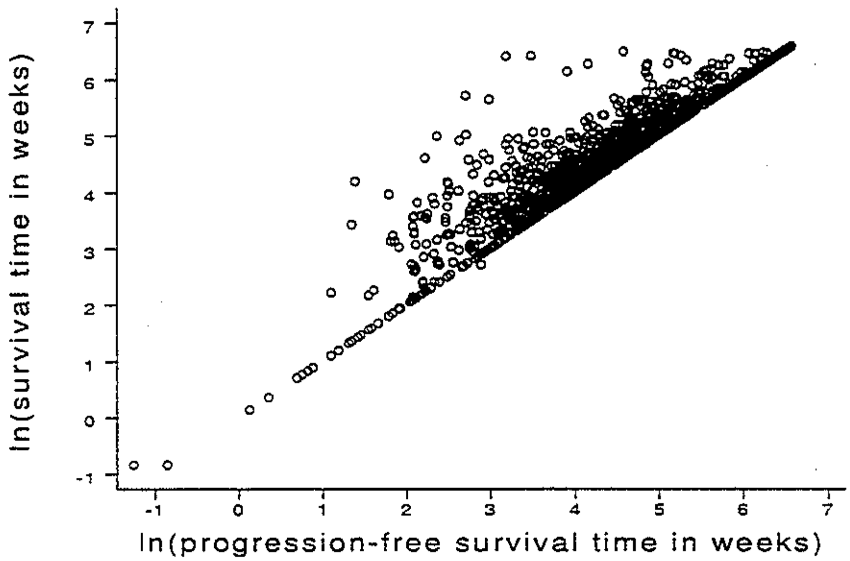
S: ***(Log of) Time to progression***

- continuous
- Time in weeks from randomization to clinical progression of the disease or death due to the disease

N: 1194

- Individual data available on every randomized patient
- 952 (80%) have died
- Censoring will be ignored

GRAPHICAL REPRESENTATION



PRENTICE'S CRITERIA

Criterion 1: Treatment Z is prognostic for surrogate S

* $S_{ij}|Z_{ij} = \mu_S + \alpha Z_{ij} + \varepsilon_{Sij}$
* $\alpha = 0.229$ (s.e. 0.091, $P = 0.013$)

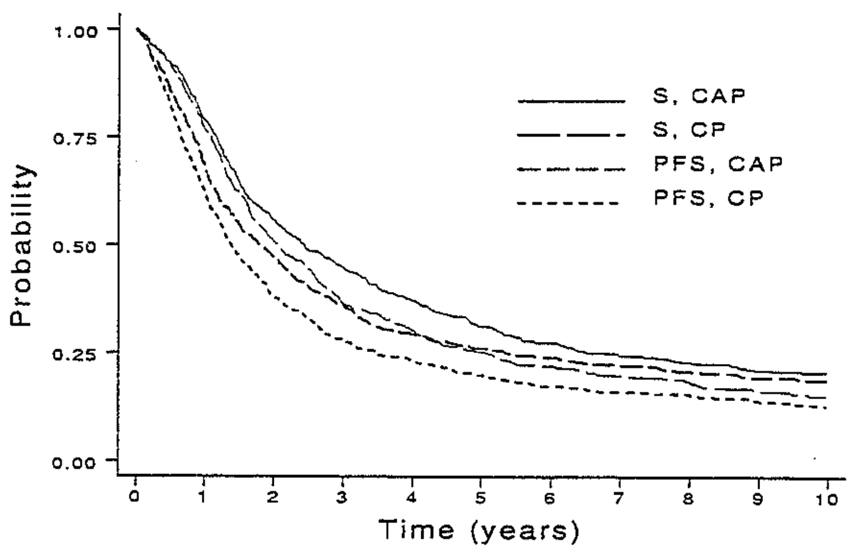
Criterion 2: Treatment Z is prognostic for true endpoint T

* $T_{ij}|Z_{ij} = \mu_T + \beta Z_{ij} + \varepsilon_{Tij}$
* $\beta = 0.149$ (s.e. 0.085, $P = 0.079$)

Criterion 3: Surrogate S is prognostic for true endpoint T

* $T_{ij}|S_{ij} = \mu + \gamma S_{ij} + \varepsilon_{ij}$
* $\gamma = 0.874$ (s.e. 0.011, $P < 0.0001$)

KAPLAN-MEIER PLOT



FREEDMAN'S PROPORTION EXPLAINED

* ***Description:***

  4. The full effect of Z on T is explained by S

* ***Model:***

$$T_{ij}|Z_{ij}, S_{ij} \quad = \quad \tilde{\mu}_T + \beta_S Z_{ij} + \gamma_Z S_{ij} + \tilde{\varepsilon}_{Tij},$$

* ***Definition:***

$$\text{PE}(T, S, Z) = \frac{\beta - \beta_S}{\beta}$$

* ***Estimate:***

  - $\beta_S = -0.051$ (s.e. 0.028)

  - $PE = 1.34$ (95% confidence limits [0.73; 1.96])

* ***But:*** problems with PE

CRITICISM

* PE not restricted to unit interval

  Volberding et al (1990)

  Choi et al (1993)

* confidence limits (Fieller or delta) tend to be wide
  - unless large sample sizes
  - unless very strong effect of Z on T
  - Lin, Fleming, and DeGruttola (1997)

* Proposal: two new criteria:
  - ***Relative Effect***
  - ***Adjusted Association***
  - Buyse and Molenberghs (1998)

RELATIVE EFFECT

* Can we link the effect of Z on S to the effect of Z on T ?

* ***Description:***

  4A. The effect of Z on S predicts a clinically useful effect of Z on T

* ***Definition:***

$$\text{RE}(T, S, Z) = \frac{\beta}{\alpha}$$

* ***Estimate:***

  - $RE = 0.61$ (95% confidence limits [0.34; 0.87])

ADJUSTED ASSOCIATION

* What is the association between S and T, after correction for Z ?

* ***Description:***

  4B. The correlation between S and T after correction for Z

* ***Definition:***

$$\rho_Z = \text{Corr}(S, T|Z)$$

* ***Estimate:***

  - $\rho_Z = 0.944$ (95% confidence limits $[0.92; 0.96]$)

MEASURES OF SURROGACY

* Criticism: PE ***not*** useful

* For normal endpoints:

$$PE = \frac{\rho_Z}{RE}$$

* The two new quantities have clear meaning
  - ***Relative Effect:*** trial-level measure of surrogacy

    Can we translate the treatment effect on the surrogate to the treatment effect on the endpoint, *in a sufficiently precise way* ?

  - ***Adjusted Association:*** individual-level measure of surrogacy

    After accounting for the treatment effect, is the surrogate endpoint predictive for a patient's true endpoint ?

* **BUT:**

  The RE is based on a single trial $\Rightarrow$ regression through the origin, based on one point !

ANALYSIS BASED ON SEVERAL TRIALS

* **Context:**
  - multicenter trials
  - meta analysis
  - several meta analyses

* **Extensions:**
  - ***Relative Effect*** $\longrightarrow$ ***Trial-Level Surrogacy***

    How close is the relationship between the treatment effects on the surrogate and true endpoints, based on the various trials ?

  - ***Adjusted Association*** $\longrightarrow$ ***Individual-Level Surrogacy***

    How close is the relationship between the surrogate and true outcome, after accounting for trial and treatment effects ?

IS CONSIDERED A USEFUL IDEA

Albert et al (1998)

There has been little work on alternative statistical approaches. A meta-analysis approach seems desirable to reduce variability. Nevertheless, we need to resolve basic problems in the interpretation of measures of surrogacy such as PE as well as questions about the biologic mechanisms of drug action.

STATISTICAL MODEL

* ***Model:***

$$
\begin{aligned}
S_{ij}|Z_{ij} &= \mu_{Si} + \alpha_i Z_{ij} + \varepsilon_{Sij} \\
T_{ij}|Z_{ij} &= \mu_{Ti} + \beta_i Z_{ij} + \varepsilon_{Tij}
\end{aligned}
$$

* ***Error structure:***
  - ***Individual level:***
    * Deviations ε_{Sij} and ε_{Tij} are correlated
  - ***Trial level:***
    * Treatment effects α_i and β_i are correlated
    * (Information from intercepts μ_{Si} and μ_{Ti} can be used as well)

STATISTICAL MODEL

* ***Model:***

$$
\begin{aligned}
S_{ij}|Z_{ij} &= \mu_{Si} + \alpha_i Z_{ij} + \varepsilon_{Sij} \\
T_{ij}|Z_{ij} &= \mu_{Ti} + \beta_i Z_{ij} + \varepsilon_{Tij}
\end{aligned}
$$

* ***Error structure:***

$$
\Sigma = \begin{pmatrix} \sigma_{SS} & \sigma_{ST} \\ & \sigma_{TT} \end{pmatrix}
$$

* ***Mixed effects:***

$$
\begin{pmatrix} \mu_{Si} \\ \mu_{Ti} \\ \alpha_i \\ \beta_i \end{pmatrix} = \begin{pmatrix} \mu_S \\ \mu_T \\ \alpha \\ \beta \end{pmatrix} + \begin{pmatrix} m_{Si} \\ m_{Ti} \\ a_i \\ b_i \end{pmatrix}
$$

* ***Error structure of random effects:***

$$
D = \begin{pmatrix} d_{SS} & d_{ST} & d_{Sa} & d_{Sb} \\ & d_{TT} & d_{Ta} & d_{Tb} \\ & & d_{aa} & d_{ab} \\ & & & d_{bb} \end{pmatrix}
$$

TRIAL-LEVEL SURROGACY

* ***Prediction:***
  - *What do we expect ?*

$$E(\beta + b_0 | m_{S0}, a_0)$$

  - *How precisely can we estimate it ?*

$$\text{Var}(\beta + b_0 | m_{S0}, a_0)$$

* ***Estimate:***
  - $R^2_{\text{trial}} = 0.940$ (95% C.I. $[0.81; 1.07]$)

TRIAL-LEVEL SURROGACY

* ***Prediction:***

$$E(\beta + b_0 | m_{S0}, a_0) = \beta + \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}^T \begin{pmatrix} d_{SS} & d_{Sa} \\ d_{Sa} & d_{aa} \end{pmatrix}^{-1} \begin{pmatrix} \mu_{S0} - \mu_S \\ \alpha_0 - \alpha \end{pmatrix}$$

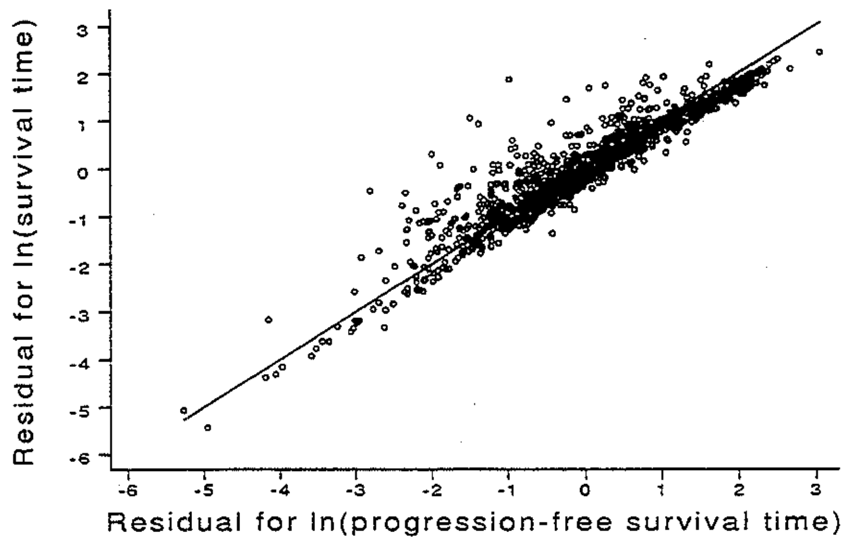
$$\text{Var}(\beta + b_0 | m_{S0}, a_0) = d_{bb} - \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}^T \begin{pmatrix} d_{SS} & d_{Sa} \\ d_{Sa} & d_{aa} \end{pmatrix}^{-1} \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}$$

* ***Trial-level association:***

$$R^2_{b_i | m_{S_i}, a_i} = \frac{\begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}^T \begin{pmatrix} d_{SS} & d_{Sa} \\ d_{Sa} & d_{aa} \end{pmatrix}^{-1} \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}}{d_{bb}}$$

* ***Estimate:***
  - $R^2_{b_i | m_{S_i}, a_i} = 0.940$ (95% confidence interval $[0.81; 1.07]$)

INDIVIDUAL-LEVEL SURROGACY



$*$ ***Trial-level association:***

$$\rho_Z = R_{\text{indiv}} = \text{Corr}(\varepsilon_{Ti}, \varepsilon_{Si})$$

$*$ ***Estimate:***

- $R^2_{\text{indiv}} = 0.887$ (95% C.I. [0.87; 0.90])
- $R_{\text{indiv}} = 0.942$ (95% C.I. [0.93; 0.95])
- Recall $\rho_Z = 0.944$ (95% C.I. [0.92; 0.96])

INDIVIDUAL-LEVEL SURROGACY

* ***Conditional density:***

$$T_{ij}|Z_{ij}, S_{ij} \sim N\{\mu_{Ti} - \sigma_{TS}\sigma_{SS}^{-1}\mu_{Si} + (\beta_i - \sigma_{TS}\sigma_{SS}^{-1}\alpha_i)Z_{ij} + \sigma_{TS}\sigma_{SS}^{-1}S_{ij}; \sigma_{TT} - \sigma_{TS}^2\sigma_{SS}^{-1}\}$$

* ***Trial-level association:***

$$\rho_Z = R^2_{\varepsilon_{T_i}|\varepsilon_{S_i}} = \frac{\sigma_{ST}^2}{\sigma_{SS}\sigma_{TT}}$$

* ***Estimate:***

  - $R^2_{\varepsilon_{T_i}|\varepsilon_{S_i}} = 0.887$ (95% confidence limits $[0.87; 0.90]$)
  - $R_{\varepsilon_{T_i}|\varepsilon_{S_i}} = 0.942$ (95% confidence limits $[0.93; 0.95]$)
  - Recall $\rho_Z = 0.944$ (95% confidence limits $[0.92; 0.96]$)

PREDICTION

unit	# patients	$\widehat{\alpha}_0$	$E(\beta + b_0 \mid a_0)$	$\widehat{\beta + b_0}$
6	17	-0.58 (0.33)	-0.45 (0.29)	-0.56 (0.32)
8	10	0.67 (0.76)	0.49 (0.57)	0.76 (0.39)
55	31	1.08 (0.56)	0.80 (0.44)	0.79 (0.45)
DAC	275	0.25 (0.15)	0.17 (0.13)	0.14 (0.14)
GON	125	0.15 (0.25)	0.10 (0.20)	0.03 (0.22)

CONCLUSIONS

* Basis for new assessment strategy:
  - trial-level surrogacy
  - individual-level surrogacy
* Requires
  - joint model for surrogate and true endpoint
  - accomodation of trial-level effects
* Methodological work needed for
  - binary responses
  - survival responses
  - heterogeneous cases